Doc Code: AP.PRE.REQ

PTO/SB/33 (07-05)

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| PRE-APPEAL BRIEF REQUEST FOR REVI   | FW                    | Docket Number    | (Optional)                 |  |  |  |  |
|---|-----------------------|------------------|----------------------------|--|--|--|--|
|   |                       | CLFR:178U        | SD1                        |  |  |  |  |
| I hereby certify that this correspondence is being electronically submitted   | Application N         | umber            | Filed                      |  |  |  |  |
| to Commissioner for Patents   | 10/695,27             | 5                | October 28, 2003           |  |  |  |  |
| on November (, 2006)  | First Named I         | nventor          |                            |  |  |  |  |
| Signature   | Bob G. Sa             | nders, et al.    |                            |  |  |  |  |
| Typed or printed David L Dadies   | Art Unit              |                  | Examiner                   |  |  |  |  |
| name David L. Parker  | 1623                  |                  | Devesh Khare               |  |  |  |  |
| Applicant requests review of the final rejection in the above-with this request.  | dentified ap          | plication. No    | amendments are being filed |  |  |  |  |
| This request is being filed with a notice of appeal.  |                       |                  |                            |  |  |  |  |
| The review is requested for the reason(s) stated on the attac<br>Note: No more than five (5) pages may be provided                                      |                       | ).               |                            |  |  |  |  |
| I am the  |                       | 5                |                            |  |  |  |  |
| applicant/inventor.   |                       |                  | Signature                  |  |  |  |  |
| assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.   |                       | rid L. Parker    |                            |  |  |  |  |
| (Form PTO/SB/96)  | Typed or printed name |                  |                            |  |  |  |  |
| attorney or agent of record. Registration number 32,165   |                       | 512              | -536-3055                  |  |  |  |  |
| - tograduor namos   |                       | Tele             | ephone number              |  |  |  |  |
| attorney or agent acting under 37 CFR 1.34.   |                       | Nove             | mber 1, 2006               |  |  |  |  |
| Registration number if acting under 37 CFR 1.34   | -                     |                  | Date                       |  |  |  |  |
| NOTE: Signatures of all the inventors or assignees of record of the entire<br>Submit multiple forms if more than one signature is required, see below*. | interest or their     | representative(s | ) are required.            |  |  |  |  |
| *Total of forms are submitted.  |                       |                  |                            |  |  |  |  |
|   |                       |                  |                            |  |  |  |  |

This collection of information is required by \$5 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the U.SPTO to process) an application. Confidentially is governed by \$5 U.S.C. 122 and \$7.05 R. 11.1, 11.4 and 14.6. This collection is estimated to take I complete a complete, including gathering, preparing, and submitting the completed application ferm to the U.SPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this insm and/or suggestions for reducing this between, about the sect to the Chief Information Officer, U.S. Peant and Trademark Office, U.S. Department of Commerce, P.O. 80x 1469, Alexandriu, VA 2231-3-146). DO NOT SEND FEES OR COMPLETED FORMS TO TIES ADDRESS. SEND TO CHIMISTOP AT IN STATE OF THE ADDRESS SEND TO CHIMISTOP AT IN STATE OF THE ADDRESS SEND TO CHIMISTOP AT IN STATE OF THE ADDRESS SEND TO CHIMISTOP AT IN STATE OF THE ADDRESS SEND TO CHIMISTOP AT IN STATE OF THE ADDRESS SEND TO CHIMISTOP AT IN STATE OF THE ADDRESS SEND TO CHIMISTOP ADDRESS SEND TO CHIMI

## Arguments in Support of Pre-Appeal Brief Request for 10/695,275

## I. Regarding the Enablement Rejection<sup>1</sup>

The Examiner rejects Applicant's claims directed toward a "method for inhibiting the growth of tumor cells in an individual comprising administering to the individual a pharmacologically effective dose of a compound" of this invention. This enablement rejection is unreasonable given that the Applicants have shown that the method of this invention does inhibit the growth of a wide variety of tumor cells. The examples and screening techniques disclosed by the Applicants are in relation to the scope of the claims based on the relative predictability of the art; therefore, the claims are enabled.

A common thread running through the arguments of this Action, as well as the arguments of the previous Actions, is that the Applicants must show that each and every compound covered by claim 1 will inhibit every possible form of cancer. This position is problematic because it applies an incorrect legal standard to the enablement requirement, and it ignores the specification of the Application and the Inventors' Declaration.<sup>3</sup> Both highlight the wide variety of cancer cells whose growth has been inhibited by the method of this invention. Routine screening, not undue experimentation, is all that a skilled artisan would need to do in order to test the applicability of this invention to other tumor cells.<sup>4</sup>

A variety of the compounds of this invention (chroman derivatives) were shown to induce apoptosis in one or more of the tumor cell lines. These examples were summarized in Tables 2-3 on pages 95-98 of the application. These tables are reproduced here:

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<sup>1</sup> Action of August 1, 2006, pages 3-6.

<sup>2</sup> See claim 1 of Application.

<sup>&</sup>lt;sup>3</sup> "Declaration of Bob G. Sanders, Ph.D. and Kimberly Kline, Ph.D., under 37 C.F.R. §1.132", November, 28, 2005.

<sup>&</sup>lt;sup>4</sup> Enablement is not precluded by the necessity for some experimentation such as routine screening. In re Wands, 858 F.2d 731, 736-37 (Fed. Cir. 1988).

|  | Table 2-1  |  |  |  |   |              |   | Table 2-2 |  |  |   |   |  |  |   |   |   |   |  |   |
|--|--|--|--|--|---|--------------|---|-----------|--|--|---|---|--|--|---|---|---|---|--|---|
| Cell Type  | IVES   | П  | 12   | 13   |   | 15           | 14  | 17        |  | Cell Type  | 8   | 19  | 110  | 11                                       | 12  |   | 13                                      | 14  | 15                                       |   |
| Cer iype   | VES  | 15                                       | 16   | 15   | 12                                      | 15           | 19  | 1/        |  |  |   |   |  | _  | ,   |   |   |   |  | _                                       |
| Breast Cancer  |  |  |  | т  | 7                                       | т            | <b>—</b>  | т         |  | Breast Cancer<br>HMEC  |   | - N   | - In   | N  | l   |   |   | N   | NT                                       | -                                       |
| MEC  | N  | N  | N  | N  | N                                       | N            | N   | N         | $\neg$   | MCF-10A  | N   | -17   |  | N  | N N   | -                                       |   |   | NT                                       | -                                       |
| 4CF-10A  | N  | N.                                       | N  | N  | N                                       | IN           | N   | IN        | _  | MDA-MB-435   | 5-10                                      | 5-10  |  | Ñ  | 5-10  |   |   |   | 20-30                                    | -                                       |
| 40A-MB-435   | 5-10   | 5-10                                     | 10-20  | 5-10   | N.                                      |              | N   | 5-10      | $\neg$   | MDA-MB-231   | 5-10                                      | 5-10  |  |  | 5-10  |   |   |   | 20-30                                    | -                                       |
| 40A-MB-231   | 5-10   | 5 - 10                                   | 10-20  | 5-10   | N                                       |              |   | 15-10     |  | MCF-7  | 10-20                                     |   |  |  | 5-10  | _                                       | N                                       |   | 20-30                                    | _                                       |
| ACF+7  | 10-20  | 5-10                                     | 20-30  | 20-30  | N                                       |              |   | 10-24     | 0  | T470   | NT  | NT  | NT   | NT                                       | NT  | 1                                       | NT                                      | NT  | NT                                       | 7                                       |
| 470  | N  | N  | N  | N  | N                                       | N.           | N   | N         | -  | Cervicul   |   |   |  |  |   |   |   |   |  |   |
| Aprical<br>46-180  | 10-20  | 1-5                                      | 5 - 1 0  | 10-20  | N                                       | <del> </del> | -   |           |  | NE-180   | 5-10                                      | 5-10  | N  | N  | 5-10  | -                                       | N                                       | N   | N  |   |
| Ovarian  | 10.20  | 1-5                                      | 3.10   | 10.20  | N                                       | N_           | N   | 5-10      | -  | Ovarian  |   |   |  | -  | -   |   | -                                       | -   |  | _                                       |
| -120   | N  | 10-20                                    | 10-20  | 10-20  | N-                                      | N            | N   | 10-20     | -  | C-170  | 10-26                                     | N   | N  | N.                                       | 10-2  | 0                                       | N.                                      | N   | N  | -                                       |
| ndomerisi  |  | 1.4.4.4                                  | 1.0.2.   | 1000   | 12-                                     | -            | -   | 10.5      | ~  | Endomecial   | 1 - 5                                     | 5-10  | N N  | N  | 5-10  | -                                       | N -                                     | N   |  | -                                       |
| L-95-2   | 10.20  | 10-20                                    | 10-209   | 10-20  | N                                       | N            | N   | 5-10      | -  | RL-95-2  | 1:5                                       | 3-10  | - N  | N.                                       | 3-10  |   | 4                                       | N.  | N  | -                                       |
| vostate  |  | 1  |  |  | 1                                       |              | -   | -         | _  | Prostate   | NT  | NT  | NT   | NT                                       | NT  |   | u <del>r  </del>                        | NT  | NT.                                      | -                                       |
|  | N  | N  | NT   | NT   |   | NT           |   |           |  | LnCaP  | 5-10                                      | 5-10  |  | N  | > 20 -  |   |   |   | NT                                       | _                                       |
|  | 5-10   | 5-10                                     | 5-10   | 5-10   |   |              | N   | 2.5-5     | _  | PC-3   | 5-10                                      | 5-10  | NT   | N  | 10-2  | 0 1                                     | V                                       | N I                                       | NT                                       | _                                       |
|  | 10-20  | 5-10                                     | S - 1 0  | S - 1 0  |   |              |   | 5-10      | -  | OU-145   | NT  | INT   | NT   | NT                                       | NT  |   | VT_b                                    | NT  | NT.                                      |   |
| OU-145<br>Colon  | 10.20  | 3-10                                     | IN!  | IN C   | INT                                     | NT           | NI.   | W.I       |  | Colon  |   |   |  |  | 1   |   | $\Box$                                  |   |  |   |
| (T-29  | 5-10   | 10-20                                    | NT   | NT   | NY.                                     | NT           | NY.   | Let .     | -  | HT-29  | NT  | NT  |  | NY                                       |   |   |   | NT I                                      |  |   |
| LO-1   | 10-20  | 10-20                                    | NT   | NT   |   | NT           |   |           | -  | 0LD-1  | NT  | NT  | NT.  | NY                                       | NT  |   | VT.                                     | NT  | VI                                       | 4                                       |
| ung  |  | 1  |  | -  | -                                       | -            | 1   | -         | _  | Luna   | -   | NT.   |  | NT                                       |   |   | -                                       | NT I                                      |  | -                                       |
| 3-549  | 20-30  | 10-20                                    | NT   | NT   | NT                                      | NT:          | NT  | NT        | _  | A-S49<br>Lymphoid Cells  | NT  | - N   | - 31   | M.                                       | NI.   |   | 4                                       |   | 4 1524                                   | -                                       |
| vmchoid Cells  |  |  |  |  |   |              | Į   | Çe.       |  | Mysloma  | NT  | NT  | NT   | NT                                       | NT  |   | J# 1                                    | NT I                                      | VT                                       | -                                       |
|  | 10-20  |  | N7   | NT   |   | NT           |   |           |  | Reil   | NT  | NT  |  | NT                                       |   | - 1                                     | VT I                                    | NT I                                      | VT                                       | -1                                      |
| af   | 10-20  | NT                                       | NT   | NT   | NY.                                     | NT           | NT  | NT        | _  | Ramos  | NT  | NT  | NT   | NT                                       | NT.   | 7                                       | VT I                                    | NT I                                      | 47                                       | _                                       |
|  |  | NT<br>1 0 - 2 0                          | NT<br>NT   | NT<br>NT   | NT                                      | NT<br>NT     | NT.   | NT        | _  |  | NT  | INT   |  | NT                                       |   |   |   | NT I                                      |  | _                                       |
|  |  |  |  |  | N                                       |              | N)  | 5-10      | _  | HL-60  | 10-20                                     | 10-2  | 0 N  | N  | 20-31   | 2_1                                     | 4                                       | N   | vī.                                      |   |
|  |  |  |  |  |   |              |   |           |  |  |   |   |  |  |   |   |   |   |  |   |
| Cel Type   |  |  | Table  | 3-1  |   |              |   |           |  |  |   | ,   | Tuble  |  |   |   |   |   |  |   |
|  | 16 117   | 118                                      |  |  | 21                                      |              | 123   |           | 23   | Cell Type  | 24  | 125   | Tuble  | 3-                                       |   | 8  2                                    | 9 [3                                    | 19  | [42                                      |   |
| Present Conces   |  |  |  |  | 21                                      |              | 122   |           | 23   | Breast Can   | er T                                      |   | 26   | 127                                      | - 2   | _                                       | _                                       | _   |  | -                                       |
| Breast Cancer  |  |  | 119  | 20   |   |              | _   |           |  | Breast Can   | er NT                                     | NY  | 26<br>NT   | I27                                      | 12  | TN                                      | T                                       | vT .                                      | NT                                       | -                                       |
| HMEC   | NT NT  | NT<br>NT                                 | NT N   | 20<br>NT   | 21<br>NT                                |              | M   | ,         | М  | Breast Cana<br>HMEC<br>MCF-10A   | er<br>NT                                  | NT<br>N   | NT<br>N  | NT<br>NT                                 | - 12  | T N                                     | TA                                      | er<br>er                                  | NT<br>NT                                 | - 1                                     |
| MCF-10A<br>MOA-NB-435  | NT NT<br>N TN  | NT<br>NT                                 | NT N 10-20   | NT<br>N<br>1 0 - 2 0   | NT<br>N                                 |              | N N   |           | ZZ<br>ZZ   | Breast Can-<br>HAVEC<br>MCF-10A<br>MOA-MB-43   | er NT                                     | NY<br>N   | 26<br>NT<br>N<br>2 0 -4 0  | NT<br>NT                                 |   | T N                                     | T A                                     | (T<br>(T                                  | NT<br>NT<br>0 10-                        | A 0 S                                   |
| MCF-10A<br>MCF-10A<br>MOA-NB-435<br>MOA-NB-231   | NT NT<br>N TN<br>N NT<br>N NT  | NT<br>NT<br>N                            | NT N 10-20   | NT N 1 0 - 2 0   | NT<br>N<br>N                            |              | N N   |           | Z z Z  | Breast Can-<br>lays C<br>MCF-10A<br>M0A-M8-41<br>M0A-M8-21   | er NT<br>NT<br>5 N                        | NT<br>N<br>N  | 26<br>NT<br>N<br>20-40   | NT<br>NT<br>NT                           | i i   | T N                                     | T A                                     | 0.2                                       | NT<br>NT<br>0 10-                        | A 0 S                                   |
| HNEC<br>MCF-10A<br>MOA-NB-435<br>MOA-MB-231<br>MCF-7   | NT NT<br>NT N<br>N NT<br>N NT<br>N 10  | NT<br>NT<br>N<br>NT                      | NT N 10-20 NT 10-20  | NT N 1 0 - 2 0 NT S - 1 0  | NT<br>N<br>N                            |              | X X X X X X X X X X X X X X X X X X X   | 5-20      | 2222   | Breast Can-<br>1975 C<br>MCF-10A<br>MOA-MB-4<br>MOA-MB-2   | er NT                                     | NY<br>N   | 26<br>NT<br>N<br>2 0 -4 0  | NT<br>NT<br>NT                           | 2<br>   | T N                                     | T A                                     | 0 -2<br>0 -7                              | NT<br>NT<br>0 10-                        | A 0 5                                   |
| HMEC<br>MCF-10A<br>MOA-NB-435<br>MOA-NB-231<br>MCF-7<br>T470   | NT NT<br>N TN<br>N NT<br>N NT  | NT<br>NT<br>N<br>NT                      | NT N 10-20   | NT N 1 0 - 2 0   | NT<br>N<br>N                            |              | N N   | 5-20      | Z z Z  | Breast Con-<br>19/5C<br>MCF-10A<br>MOA-MB-23<br>MCF-7<br>1470<br>Central   | MY<br>NT<br>S N<br>1 NT<br>N              | NT<br>N<br>N<br>NT<br>NT                                | 26<br>NT<br>N<br>20-40<br>NT   | NT NT                                    | 2<br>   | T N                                     | T N                                     | T 0-2                                     | NT<br>NT<br>0 10-<br>NT<br>NT            | A 0 S                                   |
| HMEC<br>MCF-10A<br>MOA-NB-435<br>MOA-NB-231<br>MCF-7<br>T470<br>Cervicel   | NT NT N  | NT<br>NT<br>N<br>NT<br>-20 N<br>-20 NT   | NT N 10-20 NT 10-20 N  | NT<br>N 10-20<br>NT<br>S-10<br>5-10  | NT<br>N<br>N<br>NT<br>N                 |              | NO<br>NO<br>NO<br>NO  | 5-20      | ZZZZZ  | Breast Cans<br>19/5 C<br>MCF-10A<br>MOA-HB-53<br>MCF-7<br>T470<br>Cervical<br>ME-180   | 97<br>NT<br>S N<br>1 NT                   | NT<br>N<br>N<br>NT<br>NT                                | 26<br>NT<br>N<br>20-40<br>NT   | NT<br>NT<br>NT                           | 2<br>   | T N                                     | T A                                     | T 0-2                                     | NT<br>NT<br>0 10-                        | A 0 5                                   |
| HMEC<br>MCF-10A<br>MOA-MB-435<br>MOA-MB-231<br>MCF-7<br>T470<br>Cervical<br>ME-180   | NT NT<br>NT N<br>N NT<br>N NT<br>N 10  | NT<br>NT<br>N<br>NT<br>-20 N<br>-20 NT   | NT N 10-20 NT 10-20  | NT N 1 0 - 2 0 NT S - 1 0  | NT<br>N<br>N                            |              | X X X X X X X X X X X X X X X X X X X   | 5-20      | 2222   | Breast Cans<br>1-3/F C<br>MCF-10A<br>M0A-M8-2<br>MCF-7<br>T470<br>Canscal<br>ME-180<br>Overlan   | M NT NT                                   | NT<br>N<br>N<br>NT<br>NT<br>N                           | NT<br>N<br>20-40<br>NT<br>N  | NT<br>NT<br>NT<br>NT<br>NT               | ) - 2 O N   | T N                                     | T N                                     | π<br>π<br>π<br>π<br>π                     | NT<br>NT<br>0 10-<br>NT<br>NT<br>NT      | A 0 P                                   |
| HMEC<br>MCF-10A<br>MOA-NB-435<br>MOA-NB-231<br>MCF-7<br>T470<br>Central<br>ME-180<br>Gyaran  | NT NT NT N NT N NT N NT N NT 10 NT 10  | NT<br>NT<br>N<br>NT<br>-20 N<br>-20 NT   | NT N 10-20 NT 10-20 N  | NT<br>N 10-20<br>NT<br>S-10<br>5-10  | NT<br>N<br>N<br>NT<br>N                 |              | NO<br>NO<br>NO<br>NO  | 5-20      | ZZZZZ  | Breast Cam-<br>HAVEC<br>HCF-10A<br>MOA-MB-2,<br>MCA-F7<br>T470<br>Caroscal<br>ME-180<br>Overtan<br>C-170   | M NT NT                                   | NT<br>N<br>N<br>NT<br>NT                                | 26<br>NT<br>N<br>20-40<br>NT   | NT<br>NT<br>NT<br>NT<br>NT               | ) - 2 O N   | T N                                     | T N                                     | π<br>π<br>π<br>π<br>π                     | NT<br>NT<br>0 10-<br>NT<br>NT            | A 0 S                                   |
| HMEC<br>MCF-10A<br>MOA-HR-435<br>MOA-HR-231<br>MCF-7<br>T470<br>Censical<br>Mi-180<br>Gyarlan<br>C-170<br>Endomerial   | NT NT N N NT N N NT N N 10 NT 10 NT 20   | NT N | NT<br>N<br>110-20<br>NT<br>10-20<br>N<br>1-5                             | NT N 10-20 NT 5-10 5-10  | MT<br>N<br>N<br>NT<br>N<br>MT           |              | NO<br>NO<br>NO<br>NO<br>NO<br>NO<br>NO<br>NO<br>NO<br>NO<br>NO<br>NO<br>NO<br>N | 5-20      | N N N N N N N N N N N N N N N N N N N  | Breast Can:<br>14/5C<br>MCF-10A<br>MOA-M9-21<br>MOA-M9-23<br>MCF-7<br>T470<br>Ceroical<br>MC-180<br>Overtain<br>C-170<br>Endomental  | S N I NT N NT NT NT NT                    | NT<br>N<br>N<br>NT<br>NT<br>N<br>NT                     | NT<br>N<br>2 0 -4 0<br>NT<br>N<br>N  | NT NT NT NT                              |   | T N T N                                 | T N                                     | о -2<br>о -2<br>о т<br>о т                | NT NT NT NT NT                           | 0 P<br>0 P<br>0 P<br>0 P                |
| HMEC<br>MCF-10A<br>MOA-MB-435<br>MOA-MB-331<br>MCF-7<br>T470<br>Cervical<br>ME-180<br>Gvarian<br>C-170<br>Endomerial<br>RL-95-2  | NT NT NT N NT N NT N NT N NT 10 NT 10  | NT<br>NT<br>N<br>NT<br>-20 N<br>-20 NT   | NT<br>N<br>110-20<br>NT<br>10-20<br>N<br>1-5                             | NT N 10-20 NT 5-10 5-10  | MT<br>N<br>N<br>NT<br>NT                |              | NO NO   | 5-20      | 12<br>22<br>22<br>23<br>24<br>24<br>24<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25<br>25 | Breast Cam:<br>19/9C<br>10/7-10A<br>MOA-MB-23<br>MCF-7<br>7 7470<br>Carried<br>ME-180<br>Overtan<br>C-170<br>Endomenia<br>8L 95-2  | M NT NT                                   | NT<br>N<br>N<br>NT<br>NT<br>N<br>NT                     | NT<br>N<br>20-40<br>NT<br>N  | NT NT NT NT                              |   | T N T N                                 | T N                                     | о -2<br>о -2<br>о т<br>о т                | NT<br>NT<br>0 10-<br>NT<br>NT<br>NT      | A 0 P                                   |
| HNEC<br>MCF-10A<br>MOA-NB-435<br>MOA-NB-231<br>MCF-7<br>T470<br>Centical<br>ME-180<br>Ovarian<br>C-170<br>Endomerial<br>RL-95-2<br>Prostate  | NT NT NT NT N NT N NT 10 NT 10 NT 20 NT NT NT  | NT N | NT 10-20 NT 10-20 N 1-5 NT   | NT N 110-20 NT 5-10 5-10   | NT<br>N<br>NT<br>NT<br>NT               | <u> </u>     | M NO  | 5-20      | NT NT  | Breast Cam: 14/5/10A  | es NT NT S N NT NT NT NT NT NT            | NT<br>N<br>N<br>NT<br>NT<br>N<br>NT                     | NT<br>N<br>20-40<br>NT<br>N<br>N<br>N  | NT N |   | T N T N T N T N T N T N T N T N T N T N | T N                                     | о -2<br>о -2<br>о -7<br>о -7              | NT NT NT NT NT                           | 4 A A A A A A A A A A A A A A A A A A A |
| HMSC<br>MCF-10A<br>M0A-M8-435<br>M0A-M8-231<br>MCF-7<br>T470<br>Central<br>M5-180<br>Ovarian<br>C-170<br>Endomerial<br>RL-95-2<br>Prastate<br>PSEC   | NT NT NT N N NT N N NT N N NT N N NT 2 0 NT                    | NT N | 119<br>NT<br>N<br>110-20<br>NT<br>110-20<br>N<br>11-5<br>NT              | NT N 1 0 - 2 0 NT 5 - 1 0 5 - 1 0 1 - 5 1 0 1 - 5 1 0 1 NT NT NT   | NT N NT N N N N N N N N N N N N N N N N | 3            | 2   | 5-20      | N N N N N N N N N N N N N N N N N N N  | Birrast Cani<br>1995<br>MCF-10A<br>MQA-MB-13<br>MCF-7<br>17470<br>Caronal<br>ME-180<br>Ocean<br>C-170<br>Endomenia<br>RL-95-2<br>Prostate<br>PREC  | MT NT NT NT NT NT NT NT NT NT             | NT<br>N<br>N<br>NT<br>NT<br>N<br>NT                     | NT<br>N<br>20-40<br>NT<br>N<br>20-30   | NT N | 2<br>  h<br>  h<br>  h<br>  N<br>  D-20 N<br>  N<br>  N         | T N T N T N T N T N T N T N T N T N T N | T N<br>T N<br>T N<br>T N                | 7 0-2 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | NT NT NT NT                              | N N                                     |
| HMEC<br>MCF-10A<br>MOA-M8-435<br>MOA-M8-231<br>MCF-7<br>T470<br>Cercical<br>ME-180<br>Govarian<br>C-170<br>Endometal<br>BL-95-2<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Pressate<br>Piec<br>Piec<br>Piec<br>Piec<br>Piec<br>Piec<br>Piec<br>Pie   | NT NT NT N NT N 1 0 NT 1 0 NT                                  | NT NT NT N NT | 19   | NT NT S-10  1-5  NT NT NT S-10  1-5  NT S-10  NT S-10  | NT N NT N                               | 3            | 22 22 23 23 23 23 23 23 23 23 23 23 23 2  | 5-20      | N N N N N N N N N N N N N N N N N N N  | Binast Cam<br>Invite Mc2-10A<br>MOA-M8-23<br>MC2-77<br>T-470<br>Carvical M6-180<br>Oversian C-170<br>Englowerial RL-93-2<br>Prostates<br>PREC LL-00P   | NT             | NT<br>N<br>N<br>N<br>NT<br>N<br>NT<br>N                 | NT<br>N<br>20-40<br>NT<br>N<br>N<br>N  | NT N | 2<br>  h<br>  h<br>  h<br>  N<br>  N   N<br>  NT   N<br>  N   N | T N T N T N T N T N T N T N T N T N T N | T N                                     | or<br>or<br>or<br>or<br>or<br>or<br>or    | NT NT NT NT NT NT NT NT NT               | N N N N N N N N N N N N N N N N N N N   |
| HMSC MCF-10A MCF-10A MOA-H9-435 MOA-H9-435 MOA-H9-435 MOA-H9-231 MCF-7 T470 Cornical McF-180 Goarian C-170 Resident McF-19-22 Cornical McF-180 Countries McF-180 Countries McF-180 Countries McF-180 Countries PSC Countries PSC MCF-180 MCF-1   | NT NT NT N NT N NT N NT N NT N N NT N N NT N N NT N N N NT N | NT N | 119  | NT   NT   NT   S - 1 0 * | NT N NT N NT N N N N N N N N N N N N N  |              | MO M  | 5-20      | 22 22 22 23 25 25 25 25 25 25 25 25 25 25 25 25 25   | Breast Can 14/4/C 14/5/-10/A 14/5   | NT N  | NT<br>N<br>N<br>N<br>NT<br>NT<br>N<br>N<br>NT<br>N<br>N | NT<br>N<br>20-40<br>NT<br>N<br>20-30<br>20-30  | NT N | 2<br>  h<br>  h<br>  h<br>  N<br>  N   N<br>  NT   N<br>  N   N | T N T N T N T N T N T N T N T N T N T N | T N                                     | 7 0 -2 0 0 -2 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | NT NT NT NT                              | N N                                     |
| HMEC   MCF-10A   MCF-10A   MCF-10A   MCF-10A   MCF-145   MCF-17-17470   MCF-180   MCF-180   MCF-170   MCF-170   MCF-180   MC   | NT N   | NT N | 19   | NT   NT   NT   S - 1 0 * | NT N NT N                               |              | 22 22 23 23 23 23 23 23 23 23 23 23 23 2  | 5-20      | N N N N N N N N N N N N N N N N N N N  | Breast Com-<br>144 (C. 1404 (C. 1  | NT N  | NT N N N N N N N N N N N N N N N N N N                  | NT<br>N<br>N 20-40<br>NT<br>N<br>N<br>20-30<br>20-30                                   | NT N | NT N N N N N N N N  | T N T N T N T N T N T N T N T N T N T N | T N T N T N T N T N T N T N T N T N T N | T T T T T T T T T T T T T T T T T T T     | NT N | N N N N N N N N N N N N N N N N N N N   |
| He/SC<br>MCF-10A<br>MOA-H8-435<br>MOA-H8-435<br>MOA-H8-231<br>MC-H8-231<br>ME-180<br>Gearsian<br>C-170<br>Endomerial<br>BL-95-2<br>Prostate<br>PS/C<br>InCAP<br>PC-3<br>OU-145<br>Colon  | NT N   | NT N | NT N 1 1 - 5 NT N 1 - 5 NT N N N N N N N N N N N N N N N N N             | 10   | NT<br>N<br>N<br>NT<br>N<br>N<br>N<br>N  | 3            | 60<br>80<br>80<br>80<br>80<br>80<br>80<br>80<br>80<br>80                        | 5-20      | 5 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2  | Breast Con-<br>1946C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C<br>1947C | NT N  | NT N N N N N N N N N N N N N N N N N N                  | 26<br>NT<br>N<br>20-40<br>NT<br>N<br>N<br>20-30<br>20-30<br>NT<br>10-20<br>N<br>N      | NT N | NT N N N N N N N N N N N N N N N N N N                          | T N T N T N T N T N T N T N T N T N T N | T N T N T N T N T N T N T N T N T N T N | 7 0-2                                     | NT N | 8 N N N N N N N N N N N N N N N N N N N |
| He/EC<br>MC1-10A<br>MCA-H8-435<br>MCA-H8-435<br>MCA-H8-231<br>MCA-H8-231<br>MC-170<br>Carvissi<br>MC-180<br>Currier<br>C-170<br>Rindsmeriel<br>RL-95-2<br>Prostate<br>PSEC<br>LICAP<br>PC-3<br>QU-145<br>Colon   | NT NT NT N NT N NT N NT N NT N N NT N N NT N N NT N N N NT N | NT N | NT   NT   NT   N   NT   N   NT   N   N                                   | 20   | NT N NT N NT N N N N N N N N N N N N N  | 3            | MO M  | 5-20      | 22 22 22 23 25 25 25 25 25 25 25 25 25 25 25 25 25   |  | NT N  | NT N N N N N N N N N N N N N N N N N N                  | NT<br>N<br>N 20-40<br>NT<br>N<br>N<br>20-30<br>20-30                                   | NT N | NT N N N N N N N N  | T N T N T N T N T N T N T N T N T N T N | T N T N T N T N T N T N T N T N T N T N | 7 0-2                                     | NT N | N N N N N N N N N N N N N N N N N N N   |
| He/EC<br>MC1-10A<br>M0A-M8-435<br>M0A-M8-435<br>M0A-M8-231<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal<br>M2-180<br>Convisal | NT N   | NT N | NT N 10-20 NT N 1-5 NT               | NT N 1 0 - 2 0 NT S - 1 0 - 2 0 NT S - 1 0 - 2 0 NT S - 1 0 NT S - 1 0 NT NT NT NT NT NT NT NT NT  | NT N N N N N N N N N N N N N N N N N N  | 3            | MO M  | 5-20      | NT<br>NT<br>NT<br>NT<br>NT<br>NT<br>NT<br>NT<br>NT   | Breast Con-<br>1946C<br>1946C<br>1946C<br>1946C<br>1946C<br>1946A99A99A99A99A99A99A99A99A99A99A99A99A99  | NT N  | NT N N N N N N N N N N N N N N N N N N                  | 26<br>NT<br>N<br>20-40<br>NT<br>N<br>N<br>20-30<br>20-30<br>NT<br>10-20<br>N<br>N<br>N | NT N | N N N N N N N N N N N N N N N N N N N                           | T K                                     | T N T N T N T N T N T N T N T N T N T N | 7 0.2                                     | NT N | N N N N N N N N N N N N N N N N N N N   |
| HAUSE  | NT N   | NT N | NT N 10-20 NT N 1-5 NT               | NT N 1 0 - 2 0 NT S - 1 0 - 2 0 NT S - 1 0 - 2 0 NT S - 1 0 NT S - 1 0 NT NT NT NT NT NT NT NT NT  | MT<br>N<br>N<br>NT<br>N<br>NT<br>N<br>N | 3            | MO M  | 5-20      | E  | Resat Com-<br>1995     | MT NT | NT N N N N N N N N N N N N N N N N N N                  | 26<br>NT<br>N<br>20-40<br>NT<br>N<br>N<br>20-30<br>20-30<br>NT<br>10-20<br>N<br>N      | NT N | NT N N N N N N N N N N N N N N N N N N                          | T K                                     | T N T N T N T N T N T N T N T N T N T N | 7 0.2                                     | NT N | N N N N N N N N N N N N N N N N N N N   |
| IMME V V V V V V V V V V V V V V V V V V   | NT N   | NT N | NT N 10-20 NT 10-20 NT 15-5 NT NT S-10 NT S-10 NT S-20-30                | NT N 1 0 - 2 0 NT S - 1 0 - 1 0 - 2 0 NT S - 1 0 NT  | NT N N N N N N N N N N N N N N N N N N  | 3            | MO M  | 5-20      | NT N   | Recent Con-<br>1945 - 1945  | NT N  | NT N N N N N N N N N N N N N N N N N N                  | 26<br>NT<br>N<br>20-40<br>NT<br>N<br>N<br>20-30<br>20-30<br>NT<br>10-20<br>N<br>N<br>N | NT NT NT NT                              | NT N N N N N N N N N N N N N N N N N N                          | T K T N T N T N T N T N T N T N T N T N | T                                       | T T T T T                                 | NT N | N N N N N N N N N N N N N N N N N N N   |
| IMME V V V V V V V V V V V V V V V V V V   | NT NT NT N NT   | NT N | NT N 1 10 - 20 NT 1 - 5 NT S - 10 NT | 20   NT   NT   NT   NT   NT   NT   NT   N  | NT N N N N N N N N N N N N N N N N N N  | 3            | THE   | 5-20      | MT NT  |  | NT N  | NT N N N N N N N N N N N N N N N N N N                  | 26<br>NT<br>N<br>20-40<br>NT<br>N<br>N<br>20-30<br>20-30<br>NT<br>10-20<br>N<br>N<br>N | NT NT NT NT NT NT NT                     | N N N N N N N N N N N N N N N N N N N                           | T K                                     | T A T A T A T A T A T A T A T A T A T A | T T T T T T T T T T T T T T T T T T T     | NT N | N N N N N N N N N N N N N N N N N N N   |
| He/EC MCF-10A MCA-H8-435 MCF-10A MCA-H8-435 MCC-H8-231 MCC-T7 T470 Central MC-180 Souriss C-170 H8-180 Souriss R1-85-2 Prestate PSC Color H7-29 CU-1 Lung A-549 Lung A-549 Lung A-549 Lung A-549 Lung A-549 Lung A-549 Lung  | NT N   | NT N | NT   NT   NT   NT   NT   NT   NT   NT                                    | 10   10   10   10   10   10   10   10  | NT N N N N N N N N N N N N N N N N N N  | 3            | MO M  | 5-20      | NT N   | Recent Con-<br>1945 - 1945  | NT N  | NY N N N N N N N N N N N N N N N N N N                  | 26<br>NT<br>N<br>20-40<br>NT<br>N<br>20-30<br>20-30<br>NT<br>10-20<br>N<br>N<br>N<br>N | NT NT NT NT                              | 12   15   15   15   15   15   15   15                           | T K                                     | T A T N T N T N T N T N T N T N T N T N | T T T T T T T T T T T T T T T T T T T     | NT N | N N N N N N N N N N N N N N N N N N N   |

The tables summarize the apoptotic  $EC_{50}$  for a battery of test cancer cells for the twenty-nine novel  $RR-\alpha$ -tocopherol compounds and two of the five 1-aza- $\alpha$ -tocopherol analogs of this invention. These studies indicated that a broad class of these compounds, comprising a variety of R groups are effective for arresting growth and inducing apoptosis in an equally broad variety of cancer cells. Furthermore, these studies showed that the compounds of this invention are not toxic to normal cells.

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In parallel with the *in vitro* cell culture studies, the inventors further validated the effectiveness of the chroman ring compounds in studies using mouse model systems (see Example 15, page 109 - 112 of the application). The inventors have also shown that  $\alpha$ -TEA, a model chroman ring compound, can reduce the human mammary tumor burden in mouse model systems and prevent metastasis of these cancer cells (see Table 6, page 119). In yet another example, Table 4 on page 100, the inventors showed that the amount of compound 44 needed to induce growth arrest in 50% of MDA-MB-43 tumor cells was shown to be 6 times less than the amount of compound 1 required for the same anti-proliferative activity. Applicants have therefore provided a representative group of examples of using the compounds of this invention to inhibit the growth of a diverse variety of tumor cells. These examples are in relation to the scope of the claims based on the relative predictability of the art.

The Examiner has provided no evidence that any of the claims are not enabled. Indeed, the Examiner has conceded that the claims are enabled as to:

- A "method of inducing apoptosis of a cell comprising administering an effective amount of a compound" of this invention. See Action of 09/10/2004, page 2.
- "[F]ifteen out of twenty nine RRR-α-tocopherol compounds and two out of five 1-aza-α-tocopherol analogs effective at inducing tumor cells to undergo apoptosis which having no apoptotic inducing properties on normal cells." See Action of 06/01/2005, page 2.
- "F]or in vitro screening assay to determine the effective concentration of said compounds to induce apoptosis of the cells in culture." See Action of 03/06/2006, page 2.

Given all the aspects of the invention which the Examiner concedes are enabled, the Examiner's enablement rejection of a "method for inhibiting the growth of tumor cells in an individual

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comprising administering to the individual a pharmacologically effective dose of a compound" of this invention is unreasonable. The Examiner appears to confuse the requirements under the law for obtaining a patent with the requirements under the law for obtaining FDA approval to market a particular drug to the public.<sup>6</sup>

In view of the foregoing, it is evident that the inventors' specification provides the necessary instruction for one of skill in the art to practice the invention with the class of compounds that are claimed without undue experimentation. Based on the foregoing as well as the entire file history, it is evident that this rejection will not be sustained on appeal.

## II. Regarding the 103(a) Rejection: Statement Regarding Common Ownership

The Examiner also rejected all the currently pending claims as obvious over two parent applications to which the present application claims priority, namely U.S. Patent 6,770,672 ('672) and U.S. Patent 6,417,223 ('223). According to the Examiner, both of these patents constitute prior art under 35 U.S.C. 102(e). However, in so far as the '672 and '223 patents are prior art under 102(e), they also qualify for the 35 U.S.C. 103(c) exclusion. Specifically, the undersigned counsel for the Applicants avers to the fact that the present Application, as well as the '672 and '223 patents, have at all times been owned by or subject to assignment to the same party, the Board of Regents of The University of Texas System. The Action's 103(a) rejections are therefore overcome, and should be withdrawn.

5 See claim 1 of Application.

7 Action of August 1, 2006, pages 6-9.

<sup>&</sup>lt;sup>6</sup> See In re Brana, 51 F.3d 1560,1566 (Fed. Cir. 1995).

Respectfully submitted,

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Date: November 1, 2006